PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Docket No: Q94143
Ikuo MORITA, et al.	
Appln. No.: 10/574,687	Group Art Unit: 1651
Confirmation No.: 3712	Examiner: Taeyoon KIM
Filed: April 5, 2006	

For: METHOD OF CONSTRUCTING ARTIFICIAL CELL TISSUE AND BASE MATERIAL THEREOF

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

Table of Contents

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Dai Nippon Printing Co., Ltd., by virtue of an assignment recorded on April 5, 2006, at Reel 017781, Frame 0569 in the present Application.

II. RELATED APPEALS AND INTERFERENCES

To the knowledge and belief of Appellant, the Assignee, and the undersigned, there are no other appeals or interferences before the Board of Appeals and Interferences that will directly affect or be affected by the Board's decision in the instant Appeal.

III. STATUS OF CLAIMS

Claims 1, 3-7, and 9-18 are pending, of which Claims 10-17 are withdrawn from consideration.

Claims 2 and 8 are canceled.

Claims 1, 3-7, 9 and 18 stand rejected, and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

Amendments to the claims were submitted on April 6, 2009 in an Amendment under 37 C.F.R. § 1.116 and entered on June 3, 2009 by the filing of a Request for Continued Examination.

No amendments to the claims were filed subsequent to the Final Office Action dated April 28, 2010.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 1 is the sole independent claim on appeal.

Claim 1 is directed to a method for culturing cells.

The method comprises:

causing cells to adhere to a surface of a cell array substrate having a cell adhesiveness variation pattern that comprises a first region where at least part of population of the cells adhere and a second region where the at least part of population of the cells does not adhere, to give a cell array substrate with the cells adhered to the first region in a patterned state (page 52, line 23 to page 57, line 21),

transferring the adhered cells to a cell culture substrate in the patterned state (page 57, line 24 to page 59, line 20); and

culturing the transferred cells (page 59, line 15 to page 62, line 9),

wherein the transferring step comprises removing the cells from the first region without enzymatic degradation (page 61, lines 7-12),

wherein the first region in the cell adhesiveness variation pattern has water contact angles between 10° and 40° (page 4, lines 20-22),

and wherein the cell adhesiveness variation pattern is a pattern wherein the first region is arranged on the second region, said first region being linear (page 5, lines 12-16).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1, 3-7, 9 and 18 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,324,591 to Georger, Jr. et al. ("Georger") in view of U.S. Patent 6,294,313 to Kobayashi et al. ("Kobayashi") and U.S. Patent 5,776,748 to Singhvi et al. ("Singhvi")

VII. ARGUMENT

Claims 1, 3-7, 9 and 18 are patentable over Georger in view of Kobayashi and Singhvi.

The Examiner cites Georger as teaching a method of culturing cells on patterned surfaces of an ultra-thin film (UTF) having selective adhesion formed by patterned irradiation (*see* Office Action of November 20, 2009). The Examiner cites Kobayashi as teaching TiO_2 as a photocatalyst.

The Examiner characterizes the surface of Georger in the following manner: The UTF is formed on a glass plate coated with EDA (aminosilane), and upon irradiation, the water contact angle of EDA having 28-32° is changed to 92-94° (col. 4, line 65 through col. 5, line 2), providing EDA coated UTF regions, taken to be cell adhesive regions, and pure UTF region, taken to be cell non-adhesive regions. With regard to the regions of Georger, the Examiner takes the EDA layer coated on top of the glass substrate to be a first region (EDA coating; cell adhesive region) formed on a second region (UTF; cell non-adhesive region).

The Examiner takes the position that because the UTF can be used as surfaces for body implants (col. 4, lines 19-21), contact of UTF containing cells on a cell adhesive region to the body as an implant would inherently transfer cells within the scope of the claims.

Also, Singhvi is cited as teaching a transfer step of cells grown in pattern on a hydrophobic/biophilic surface made of self-assembled monolayer (SAM).

In the Office Action of November 20, 2009 (page 5), the Examiner contends that it would have been obvious to try the transfer process taught by Singhvi for the cells grown on EDA UTF

of Georger on a secondary substrate having higher affinity than the hydrophobic interaction of the cells with EDA UTF.

The Examiner contends that the implantation of cells grown on cell adhesive region (EDA UTF) of Georger is considered to be the same procedure as transferring cells to another substrate having higher affinity to the cells. The Examiner reasons that cell-cell interaction is mediated by various mechanisms including cell adhesion molecules, carbohydrate-carbohydrate interaction, ligand-receptor interaction, etc., known to be much stronger than the hydrophobic interaction of Georger or Singhvi.

Subsequent to Appellants arguments submitted in the Response of February 22, 2010 (which are restated below), the Examiner contends that it would have been obvious to try the transfer step of Singhvi in the method of Georger based on the alleged similarity of "context" with a reasonable expectation of success (*see* Office Action of May 20, 2010, pages 7-8 and Office Action of November 26, 2010, page 4).

Figure 3 is cited as teaching the pattern formed on the UTF being linear.

Appellants respectfully traverse and submit that the present claims are patentable over the alleged combination of Georger, Kobayashi, and Singhvi.

Appellants explain as follows.

Georger does not teach or suggest the claimed step of transferring.

As recognized by the Examiner, Georger does not teach or suggest the step of transferring adhered cells to a cell culture substrate in a patterned state (*see* Office Action of May 20, 2010 at page 6, last full paragraph).

The reasons for rejection include a contention that Georger *inherently* transfers cells grown on UTF (*see* Office Action of May 20, 2010 at page 3, third full paragraph). However, the Examiner has not provided "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Nakashima*, 93 USPQ2d 1834, 1849 (BPAI 2010), citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990).

To the contrary, Georger teaches that the device is designed "to influence the subsequent development of tissue on or inside the device" and "might be a surgical implant material used as an artificial ligament or bone material" (col. 8, lines 3-17). Accordingly, Georger does not teach or suggest a step of transferring as claimed. Instead, the cells arrayed on the UTF surface remain on that surface, which is incorporated into the recipient as an implant material. The cells remaining on the UTF surface are not "transferred" as alleged by the Examiner.

Furthermore, as evidenced by positions taken by the Examiner during prosecution (*see* Office Action of November 26, 2010 and Advisory Action of April 8, 2011) as well as the Examiner's express acknowledgement (*see* Office Action of May 20, 2010 at page 6, last full paragraph), Georger does not teach or suggest the claimed transferring step. The rejection relies on the disclosure of Singhvi to allegedly remedy the recognized deficiency.

Kobayashi does not cure the deficiencies of Georger in this regard, and for the reasons that follow, Singhvi also does not cure the deficiencies of Georger.

Singhvi does not teach or suggest the claimed step of transferring cells *in the patterned state* as recited in Claim 1.

Although the Examiner cites columns 17 and 18 of Singhvi for the proposition that the cells of Singhvi having "specified coordinates" are in a patterned state (*see* Advisory Action of April 8, 2011 and Office Action of November 26, 2010 at page 3), the technical disclosure of Singhvi is directed to cells in an individual state rather than cells in a patterned state.

The method of Singhvi details identifying individual cells (col. 17, lines 8-11), binding individual cells (col. 17, line 16), and retrieving individual cells (col. 17, line 42). Singhvi specifically teaches that "the present invention provides for...isolating and manipulating particular individual cells which are present on a plate containing a great multiplicity of cells separated one from another by only a few microns" (col. 17, lines 45-47). That is, Singhvi teaches the transfer of one or more cells from a library to a secondary plate.

The Examiner responds that Singhvi is directed to transferring multiple cells "including entire patterned cells on the primary plate with the specified coordinate" (*see* Advisory Action of April 8, 2011). As noted by the Examiner, Singhvi teaches secondary plates that "would retrieve more than one cell by constructing a secondary plate" (Singhvi, col. 18, lines 8-12, cited in the Office Action of November 26, 2010 at page 3). However, the mere plurality of cells taught by Singhvi does not transform cells from being in an individual state to being in a patterned state.

Rather, the cited embodiment of Singhvi is directed to the transfer of a plurality of individual cells (each of technically differing character) onto a secondary plate in a manner that one of ordinary skill in the art would not consider to be "a patterned state," and more

particularly, would not consider to be the patterned state as claimed. More specifically, Singhvi teaches a cell retrieval system (col. 18, line 19) that provides for contacting a secondary plate at a specified island having specified coordinates for retrieval. In contrast, Claim 1 recites a step of transferring the adhered cells to a cell culture substrate in the patterned state defined by the variation pattern comprising a first region and a second region as recited in Claim 1. Claim 1 recites "cells adhered to the first region in a patterned state… [and a step of] transferring the adhered cells to a cell culture substrate in the patterned state."

Contrary to the Examiner's position, the cells of Singhvi are not *per se* in the patterned state recited in Claim 1 for having "specified coordinates" as the Examiner asserts.

Similarly, simply retrieving more than one cell from an island of Singhvi does not constitute transferring adhered cells in a patterned state. Further, simply retrieving more than one cell does not constitute transferring adhered cells in the patterned state as claimed.

Also, regarding the cells having specified coordinates so as to allegedly be in the claimed patterned state, one of ordinary skill in the art would recognize that the cells of the various specified coordinates would not be suitable for culturing together "in the patterned state" as recited in Claim 1.

From a slightly different perspective, Appellants dispute the Examiner's characterization of Singhvi with respect to "generating surfaces for tissue culture, creation of artificial tissues for grafting or implantation, for generating artificial tissues to adhere to the surfaces of prosthetic or implantable devices" as well as the Examiner's assertion that the patterned cells can be

transferred to the surfaces of prosthetic or implantable devices (Office Action of May 20, 2010 at page 3).

It is acknowledged that Singhvi discloses at column 20, lines 27 to 30 that the surfaces of prosthetic or implanted devices or tissue culture plates can be patterned with **patterned proteins**. However, this disclosure refers only to patterned proteins. Singhvi does not teach or suggest how to transfer a **linear cell pattern** into the surfaces of prosthetic or implanted devices or tissue culture plates. Rather, as explained *infra*, the disclosure at column 18, lines 8-18 of Singhvi teaches away from transferring a **linear cell pattern** onto a second surface.

One of ordinary skill in the art would not have modified the cited references as alleged.

Appellants respectfully disagree with the reasons for combining Georger and Singhvi as alleged by the Examiner.

First, one of ordinary skill in the art reading Singhvi would not have applied the step of transferring individual cells to the teaching of Georger.

Singhvi is directed to a device for adhering cells in a specific and predetermined position (Abstract). The embodiment relied upon by the Examiner requires a specific special orientation of the primary plate, *e.g.*, a 10 x 10 array of 100 islands, for retrieving individual cells. The transfer of cells from the primary plate to the secondary plate in Singhvi is for the purpose of selecting individual cells positioned on islands of specified coordinates (see, col. 17, ln. 48-49 and 53-57; col. 18, ln. 23-29). The cell retrieval system of Singhvi functions to retrieve particular individual cells from amongst a high density plate of a great many cells that would otherwise be an arduous and difficult task (col. 18, ln. 38-45). Accordingly, the transfer step

disclosed in Singhvi is rendered useless where desired cells are not identifiably segregated on the islands of the primary plate. Consequently, one of ordinary skill in the art would not have used the transfer step of Singhvi with the patterned substrate (see, *e.g.*, Fig. 3A) of Georger, which does not teach a library of particular individual cells.

Second, one of ordinary skill in the art would readily appreciate the fundamental difference between outgrowth in a cell culture and segregation of individual cells.

The transfer step disclosed in Singhvi is expressly applied to cells identifiably segregated on the islands of the primary plate (see, col. 17, ln. 48-49 and 53-57; col. 18, ln. 23-29). In contrast, Georger does not segregate individual cells on the patterned substrate (see, e.g., Fig. 3A) and, instead, Georger is directed to the outgrowth of cells in a cell culture. Accordingly, one of ordinary skill in the art would not have modified the cited references in the manner alleged by the Examiner.

Third, Singvhi teaches away from the detachment of cells adhered to each other in sheets. Given the objective of Singhvi for adhering cells in a specific and predetermined position (*see, e.g.,* Abstract), detachment of cells in large sheets from the substrate is disparaged. Specifically, Singhvi teaches that the size of islands should be selected to prevent formation of large sheets of cells that would be subject to detachment (col. 13, ln. 7-10 and 59-63).

Accordingly, one of ordinary skill in the art would not have applied a transfer step of Singhvi to a patterned substrate of Georger as alleged by the Examiner.

The Examiner has set not forth a *prima facie* case of obviousness.

First, Appellants submit that the basis of the Examiner's rationale for rejecting the claims is not technically sound. The Supreme Court stated that, in considering obviousness, "analysis should be made explicit…there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 82 USPQ2d 1385, 1396.

In particular, Appellants disagree with the Examiner's technical assertion that cells adhere to the surface of EDA by means of *weak hydrophobic* interactions. The Examiner contends that cells are adhered to the EDA based patterned substrate by hydrophobic interaction and so would transfer to a surface having higher binding affinity. However, EDA has an amino group, which is a *hydrophilic* moiety and exists in an ionized form under usual cell culture conditions. The cell surfaces have many proteins, which carry a negative net charge. It appears that the charges of EDA and proteins interact with each other to cause the adhesion of the cells to the UTF. In addition, US 2002/0095219 to Nelles et al., which formed the basis of an earlier rejection subsequently withdrawn, suggests that EDA has a cell adhesion promoter (column 8, lines 27 to 30). It is not reasonable to assume, as does the Examiner, that the interaction between a cell and EDA with a cell adhesion promoter is a *weak hydrophobic* interaction.

Accordingly, the Examiner's rationale for rejecting the claims is not technically sound and does not support *prima facie* obviousness.

Second, although the rejection relies on an "obvious to try" rationale, the Examiner has set not forth a *prima facie* case of obviousness. As explained by the Federal Circuit, obvious to

try analysis must satisfy the "*KSR* prong requiring the field of search to be among a 'finite number of identified' solutions." *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 575 F.3d 1341, 1347, 91 USPQ2d 1569, 1573 (Fed. Cir. 2009).

However, the Examiner has not articulated any finding that there had been a finite number of identified, predictable potential solutions to a recognized need or problem. See also MPEP 2143, Exemplary Rationale E. That is, the Examiner has not articulated a finite number of identified solutions from which one of ordinary skill in the art allegedly would have chosen.

Singhvi teaches away from the method recited in Claim 1.

The method of Claim 1 is directed to a method in which the cell adhesiveness variation pattern on the surface of the cell array substrate is a pattern having a **linear** first region (a cell adhesive region).

On the contrary, the primary plate taught in Singhvi from which individual cells are retrieved has a plurality of biophilic "islands" on its surface. Singhvi defines, at column 11, lines 32-34, that the "islands" are regions of biophilic SAM surrounded by biophobic SAM. It is evident that the "islands" of Singhvi have different shapes from the **linear** cell-adhesive regions claimed in the present invention.

The Examiner relies on the disclosure of Singhvi at column 18, lines 8-18 as evidence showing that cells on multiple islands (which the Examiner characterizes as a type of cell pattern) can be transferred at the same time to a second plate (Office Action of November 26, 2010 at page 3). However, the referenced disclosure is still directed to "islands" only and is not relevant to the **linear** cell-adhesive regions of the present invention.

No motivation

Accordingly, Singhvi provides no motivation for one of ordinary skill in the art to apply the cell-transferring (cell-retrieval) technique taught by Singhvi for transferring cells cultured on a **linear** cell-adhesive region to a cell culture plate.

Teaching away

Rather, Singhvi clearly teaches away from transferring a cell pattern cultured on a **linear** cell-adhesive region to a cell culture plate.

Specifically, the Singhvi teaches at column 12, line 62 to column 13, line 1:

> The size of the islands should be chosen such that it is not so large as to admit binding of more than one cell per island. In some circumstances, such as when it is desired to remove the cells by elution or for replica plating, a smaller size may be chosen so that the cells have less contact area with the biophilic SAM and are more easily removed. (emphasis added)

The above-excerpted portion of Singhvi clearly teaches away from using the cell-transferring technique for transferring a cell pattern cultured on a **linear** cell-adhesive region to a cell culture plate. This is because the size of the **linear** cell-adhesive region would inevitably be so large as to admit binding of more than one cell per island. Further, the above-excerpted portion clearly teaches that for the purpose of retrieving cells, **islands** need to be so small that cells have less contact area with the biophilic SAM. One of ordinary skilled in the art reading Singhvi would readily understand that a **linear** cell-adhesive region would have a size that is

inevitably much larger than **islands** and therefore cells on it must have large contact area, and that such a **linear** cell-adhesive region could not be used for the cell-transferring technique taught in Singhvi.

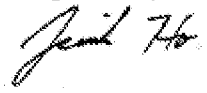
In addition, the disclosure of Singhvi at column 18, lines 8-18 would not suggest to one of ordinary skill in the art to use the technique of the document for transferring a cell pattern cultured on a **linear** cell-adhesive region, since, as stated above, Singhvi is directed to **islands** only.

VIII. CONCLUSION

Because neither Georger nor Singhvi teach or suggest all the features of Claim 1, because one of ordinary skill in the art reading the cited references would not have modified them as alleged by the Examiner, because the Examiner has not set forth a case of *prima facie* obviousness, and because Singhvi teaches away from the claimed invention, Appellants respectfully request the Board to reverse the rejection of Claims 1, 3-7, 9 and 18 over Georger in view of Kobayashi and Singhvi.

The fee required under 37 C.F.R. § 41.37(a) and 1.17(c) is being remitted. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Jerrick J. Ho
Registration No. 63,763

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: September 29, 2011

CLAIMS APPENDIX

CLAIMS 1, 3-7, 9 and 18 ON APPEAL:

1. A method for culturing cells, which comprises the steps of:

causing cells to adhere to a surface of a cell array substrate having a cell adhesiveness variation pattern that comprises a first region where at least part of population of the cells adhere and a second region where the at least part of population of the cells does not adhere, to give a cell array substrate with the cells adhered to the first region in a patterned state,

transferring the adhered cells to a cell culture substrate in the patterned state; and

culturing the transferred cells,

wherein the transferring step comprises removing the cells from the first region without enzymatic degradation,

wherein the first region in the cell adhesiveness variation pattern has water contact angles between 10° and 40°,

and wherein the cell adhesiveness variation pattern is a pattern wherein the first region is arranged on the second region, said first region being linear.

3. The method according to claim 1, wherein the cell adhesiveness variation pattern is formed of a cell adhesiveness variation layer that comprises a cell adhesiveness variation material whose cell adhesiveness is varied by the action of a photocatalyst along with energy irradiation.

4. The method according to claim 3, wherein the cell adhesiveness variation layer is a photocatalyst-comprising cell adhesiveness variation layer that comprises a photocatalyst and the cell adhesiveness variation material.

5. The method according to claim 3, wherein the cell adhesiveness variation layer comprises a photocatalyst-comprising photocatalyst treatment layer and a cell adhesiveness variation material layer that comprises the cell adhesiveness variation material formed on the photocatalyst treatment layer.

6. The method according to claim 3, wherein the cell adhesiveness variation pattern is formed by arranging the cell adhesiveness variation layer that comprises the cell adhesiveness variation material and the photocatalyst-comprising layer so that the layers face each other, and then carrying out energy irradiation.

7. The method according to claim 1, wherein the cell culture substrate is made of a biomaterial.

9. The method according to claim 1, wherein the cell adhesiveness variation pattern is a pattern wherein the first region, which is linear, and a space comprised of the second region are arranged alternately, the line width of the first region is between 20 μm and 200 μm, the space

widths between such lines are each between 300 μm and 1000 μm, and the cells used are vascular endothelial cells.

18. The method of according to claim 1, wherein the cells are comprised of two or more types of cells and the cell adhesiveness variation pattern comprises two or more of the first regions to which at least one type of the cells adhere, and two or more of the second regions to which the at least one type of the cells do not adhere.

EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix), submitted herewith are copies of any evidence submitted pursuant to 37 C.F.R. §§ 1.130, 1.131, or 1.132 or any other evidence entered by the Examiner and relied upon by Appellant in the appeal.

NONE

RELATED PROCEEDINGS APPENDIX

Submitted herewith are copies of decisions rendered by a court or the Board in any proceeding identified about in Section II pursuant to 37 C.F.R. § 41.37(c)(1)(ii).

NONE

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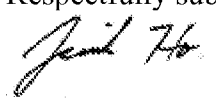
SUBMISSION OF APPEAL BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith please find an Appeal Brief. The statutory fee of $540.00 is being remitted. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Jerrick J. Ho
Registration No. 63,763

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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